

Alternative Pharmacological Management of Vasopressor Extravasation in the Absence of Phentolamine

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ABSTRACT

Vasopressor extravasation is a rare adverse drug reaction that can lead to tissue damage, ischemia, and necrosis of the affected area when vasopressors are administered peripherally. Phentolamine, a nonselective, reversible alpha antagonist, is the current standard treatment for this adverse reaction, but it is often unavailable for use. This review seeks to synthesize the available data in order to recommend alternative pharmacological options for use when phentolamine is not available. After an extensive literature search, 16 publications were reviewed. A treatment algorithm was created that recommends a combination of subcutaneous terbutaline, a selective beta₂ agonist, and topical nitroglycerin, an organic nitrate, for adults; and topical nitroglycerin monotherapy for children younger than 2 years of age. However, further research and case reports are required in order to establish a new standard of care for the treatment of vasopressor extravasation.

Keywords: vasopressor extravasation, critical care, emergency medicine, phentolamine

INTRODUCTION

Extravasations are common manifestations of iatrogenic injury that can result from intravenous (IV) delivery of known vesicants, such as vasopressors or chemotherapeutic agents. Extravasation occurs if an infused drug leaks out of the blood vessel into the surrounding tissue, possibly leading to tissue damage, ischemia, and even necrosis. Although this reaction is rare, when it does occur, the effects can be devastating if not appropriately managed. Nonpharmacological interventions are essential for extravasation management. These include immediate discontinuation of the vasopressor infusion, aspiration of any remaining fluid in the catheter, saline irrigation, elevation of the affected area, and application of warm compresses to reduce symptoms and minimize further complications.¹⁻⁵ Depending on the severity of ischemia, debridement of necrotic tissue may be necessary.

Phentolamine mesylate, dosed at 5–10 mg in 10 mL of saline injected into the area of extravasation within 12 hours, is the only pharmacological treatment for vasopressor extravasation approved by the Food and Drug Administration.⁶ It is a nonselective, reversible, alpha₁ antagonist that vasodilates vascular smooth muscles, opposing the effect of vasopressor extravasation. In the recent past, national shortages have affected the availability of phentolamine, leaving pharmacists with limited pharmacological options. The purpose of this article

is to summarize the literature supporting pharmacological alternatives available in the United States for the management of vasopressor extravasation.

LITERATURE SEARCH AND SELECTION

A literature search was performed through Medline (1946 through April 2017), Embase (1980 through April 2017), and International Pharmaceutical Abstracts (1970 through April 2017). Search terms included, “extravasation OR infiltration OR tissue ischemia OR tissue injury OR necrosis” and “norepinephrine OR noradrenaline OR epinephrine OR adrenaline OR dopamine OR vasopressin OR vasopressor OR vasoactive OR vesicant.” This combined search was then limited to “humans.” This search provided 7,367 publications, which were manually reviewed for selection of relevant references. This search was repeated with the terms “terbutaline OR nitroglycerin” included to find further references for these options. These were included as they were the predominant treatment options seen in the original search. This subsequent search returned 73 publications, which were also manually screened. Lastly, the references of selected publications and previously published reviews^{5,7} were screened to find any additional references not previously identified with the original searches. The search results were ultimately narrowed to 16 publications that were considered for this review. The most common reasons for exclusion included publications unrelated to our topic, extravasation with nonvasopressor vesicants, or discussion of treatments that included phentolamine monotherapy. All article types were eligible for inclusion; the final articles included eight case reports, three case series, three review articles, one prospective study, and one retrospective review.

ADRENERGIC RECEPTORS AND VASOPRESSOR PROPERTIES

Norepinephrine, epinephrine, phenylephrine, dopamine, and vasopressin are the vasopressors used in septic shock. Norepinephrine, epinephrine, and dopamine have various affinities for the alpha and beta receptors, while phenylephrine is mainly an alpha₁ agonist.⁸ Vasopressin is devoid of any activity on the adrenergic receptors and exerts its vasoconstriction through stimulation of V1 receptors. While vasoactive agents affect adrenergic receptors throughout the body, the alpha₁ receptor is the main receptor involved with extravasation, as it is predominantly located in the peripheral vasculature.⁸⁻¹⁰

RISK FACTORS FOR EXTRAVASATION

Many infusion-, drug-, or patient-related factors can increase the risk of vasopressor extravasation. Infusion-related factors include rapid rate, high volume, and prolonged or peripheral

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administration. Drug-related factors include solution concentration, pH less than 5.5 or greater than 8.5, and osmolarity greater than 290 mosmol/L.¹¹ All of the vasopressors are in acidic solutions with pH ranging from 2.2 to 6.5.¹² Patient factors, such as age, hemodynamic instability or hypotension (i.e., shock), and disease states with decreased perfusion to the periphery (i.e., peripheral vascular disease, diabetes mellitus, Raynaud's disease), increase risk of extravasation.⁵ Elderly patients as well as neonates are particularly prone to extravasation due to decreased blood flow to the extremities.⁵ For all of these reasons, central lines are often favored over peripheral administration of vasopressors. It is not always possible to obtain central access quickly enough in emergency and critical care settings. Consequently, peripheral administration may be unavoidable in the interim.

MANAGEMENT OPTIONS

Data are limited for the management of vasopressor extravasation in the absence of phentolamine. Case reports are the most compelling evidence currently available. After a thorough review of the literature, topical nitroglycerin and subcutaneous (SC) terbutaline are two potential alternatives that can be utilized.

Topical Nitroglycerin

Nitroglycerin is an organic nitrate that causes free-radical nitric oxide to form. Nitric oxide activates guanylate cyclase, which increases guanosine 3'5'monophosphate and leads to dephosphorylation of myosin light chains. The dephosphorylation causes vascular smooth muscle to relax, resulting in venous and arterial dilation.¹³

Topical nitroglycerin 2% ointment use for extravasation and tissue ischemia has been described in seven case reports.^{14–19} The majority of these cases involved neonatal extravasation, four caused by peripheral dopamine infusion^{14–16} and one with dopamine and dobutamine infused via umbilical arterial line.¹⁸ Two adult cases involved accidental administration of epinephrine via an autoinjector into the thumb.^{18,19}

Topical Nitroglycerin in Neonates

Nitroglycerin 2% ointment was immediately successful in three cases^{15–17} and required multiple applications in two cases.^{14,16} The time from initial presentation to initiation of treatment ranged from less than one hour up to nine hours. In addition, the amount of nitroglycerin ointment applied varied. One inch of ointment was applied to the area in one case;¹⁵ 4 mm/kg of ointment in two cases;¹⁷ enough ointment to cover the affected area in one case;¹⁵ and enough ointment to cover the area right above the line of pallor in one case.¹⁴

Immediate success was achieved in a neonate who experienced two locations of extravasation due to repositioning of the infusion after initial extravasation, the hand up to the forearm and the ankle up to the knee. When enough nitroglycerin ointment to cover the affected area was applied to both locations, about four hours later for one and nine hours later for the other, symptoms resolved within minutes. Remaining edema was resolved with a splint placed on the hand and elevation of the legs. It is not known whether warm compresses were applied throughout treatment.¹⁴

In one instance, nitroglycerin was successful in the setting of phentolamine treatment failure. Ischemia and pallor stretched from the wrist to the chest, and phentolamine failed to relieve symptoms when it was administered 30 minutes after onset. It is unknown whether warm compresses were applied. One hour later, 4 mm/kg of nitroglycerin ointment was applied, and full symptomatic resolution was noted within 15 minutes.¹⁶

The case involving a combination of dopamine and dobutamine differed slightly from the others because the infusion was administered via umbilical arterial line. Weak tibial and femoral pulses in the left leg and cyanosis in the left leg, penis, and scrotum were noted. Elevation and heat were tried unsuccessfully on the opposite leg, as well as heparin and dextran. An hour later, nitroglycerin ointment was applied along the femoral artery and at three other locations along the affected leg. Full resolution of symptoms was seen in 45 minutes.¹⁷

Other cases required multiple applications before symptoms resolved.^{14,16} One neonate required approximately one month of nitroglycerin (4 mm/kg) application just above the line of pallor, every eight hours. Slow resolution was seen each day, as symptoms began on the palm of the hand and fingers, then decreased to two fingers by day 8, and to just the fingertips on day 18. Nitroglycerin was discontinued by day 27, but full symptomatic resolution was not noted until eight months later.¹⁴ It is unclear whether the nitroglycerin or simply time played a bigger role in the resolution. This case differed from the others because the ointment was applied at the line of pallor, rather than on the entire affected area, which may explain the reduced effectiveness. Another case exhibited delayed treatment success as slight improvement was only noted eight hours after 4 mm/kg of nitroglycerin was applied and the forearm was elevated.¹⁶ Two subsequent doses were applied eight hours apart and complete resolution followed about 24 hours later.¹⁶ In both of these cases, it is unknown whether warm compresses were applied throughout treatment.

Overall in neonates, nitroglycerin seemed to be relatively safe, as adverse effects were not prominent. One patient experienced slight tachycardia and reductions in mean arterial pressure after treatment; however, the patient was hemodynamically unstable at baseline. Therefore, these cardiovascular effects cannot be attributed solely to the nitroglycerin.¹⁶

Topical Nitroglycerin in Adults

Two case reports described the use of nitroglycerin in adults after accidental digital epinephrine injections.^{18,19} Both patients experienced symptoms of pallor, decreased capillary refill, pain, loss of sensation, and eventual numbness, and the affected tissue was cool to the touch. The first case was in a 68-year-old patient who received treatment within 20 minutes with warm water, which was unsuccessful. After subsequent application of nitroglycerin, capillary refill was slowly restored four to five hours later. Sensation in the thumb was not fully recovered by the time of discharge and follow-up was not noted.¹⁸ The second epinephrine case, which affected the thumb, wrist, and forearm, occurred in a 41-year-old patient who received treatment within one hour of injection. Topical nitroglycerin was applied twice, two hours apart, but provided no symptomatic relief. Symptoms began to resolve only when heat packs were applied, and full symptom resolution was not noted until the subsequent day.¹⁹

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A prospective study was conducted at the Long Island Jewish Medical Center to evaluate the safety of peripherally administered vasoactive medications. Of 734 patients (72 ± 15 years of age) who received peripherally infused vasopressors, 19 experienced extravasation (16 due to norepinephrine and three due to dopamine). A combination of phentolamine and topical nitroglycerin paste was administered to all affected patients and complete symptom resolution was noted.²⁰

Subcutaneous Terbutaline

Terbutaline is a selective β_2 agonist. Stimulation of β_2 receptors in the vasculature causes vasodilation. Pharmacologically, this mechanism would make terbutaline a potential option for the management of vasopressor extravasation as it can dilate the β_2 -mediated vasoconstriction in the peripheral vasculature, allowing for increased blood flow and reduction in tissue ischemia.

One case series reported four patients in whom terbutaline was used for extravasation of various vasopressors in the absence of phentolamine.²¹ One of the cases involved dopamine and dobutamine, while the other three involved accidental digital epinephrine injections. Each case differed slightly, but overall treatment success occurred, with no residual effects, in three of the four cases. No adverse reactions were noted.

In the case involving dopamine and dobutamine extravasation, a 65-year-old patient experienced swelling and pallor in his hand and wrist, so the infusion was stopped. Immediate and complete resolution of symptoms occurred after a 10-mL SC injection of diluted terbutaline (1 mg/10 mL) was administered within one hour of symptom onset. The use of nonpharmacological measures was not mentioned.²¹

The other three cases, involving patients 13 to 39 years of age, involved accidental administration of epinephrine (0.3 mg/0.3 mL) into the pad of the thumb via autoinjector.²¹ All three patients experienced swelling, pallor, pain, decreased sensation, and decreased capillary refill. Each of the three cases used terbutaline for treatment; however, they differed in dosage, concomitant adjunctive therapy, and sequence of therapies trialed. The first case used 0.3 mg of diluted terbutaline (1 mg/10 mL) as the primary agent, which restored color and perfusion within two to three minutes. Despite improvement, subsequent adjunct topical nitroglycerin was applied, leading to full symptomatic resolution. It is unknown whether warm compresses were utilized. In the second case, topical nitroglycerin and warm compresses were applied. However, due to lack of response, 0.5 mg of terbutaline (1 mg/1 mL) was injected with immediate success.²¹ The last case noted no symptomatic response to 0.5 mg of terbutaline (0.5 mg/1 mL) administered twice, 15 minutes apart, for a total of 1 mg. Administration of phentolamine by digital block was eventually required to relieve symptoms. However, use of nonpharmacological interventions was not specified.²¹ Despite the differences in the therapeutic approach, these cases illustrate the importance of prompt intervention. The patient who did not symptomatically improve received relatively delayed treatment, within six hours of the original incident, while therapy was administered within the first one to two hours in the other patients.²¹

In a retrospective cohort study, authors reviewed six years worth of accidental digital injections via epinephrine

autoinjectors in the Texas Poison Center Network database.²² Patients ranged in age from 8 months to 69 years, with about 48% being older than 12 years of age. Of the 127 patients who were followed after finger injections, 29 required treatment of the area. The majority of these patients were treated with nitroglycerin paste (19 of 29), while the others were treated with phentolamine (seven of 29), a combination of nitroglycerin paste and phentolamine (two of 29), or terbutaline local injection (one of 29). Patients in all treatment groups fully recovered and had complete resolution of symptoms. Further detail was not provided about the timing of administration, timing of recovery, or use of nonpharmacological interventions.

Other Therapies

Although there are multiple case reports describing the use of topical nitroglycerin ointment for vasopressor extravasation, there are no published data supporting the use of injectable nitroglycerin for this purpose. However, injectable nitroglycerin has been used successfully in the treatment of radial artery spasm.²³ The data for topical nitroglycerin are promising; therefore, it would be reasonable to think that local injection into the site of extravasation may be even more efficacious. However, due to lack of data it cannot be recommended at this time.

Other options, such as papaverine, procaine, hyaluronidase, and conivaptan, have been tried and found to be unsuccessful in previous cases and should therefore be avoided for the treatment of vasopressor extravasation.⁵

DISCUSSION AND RECOMMENDATIONS

It is evident that vasopressor extravasation can have a rapid and unexpected onset that can be detrimental if left untreated. Unfortunately, the pharmacological standard of care, phentolamine, is far too often unavailable for use, and there is no well-studied alternative at this time. It is important that we identify a safe and effective alternative to use when this situation arises.

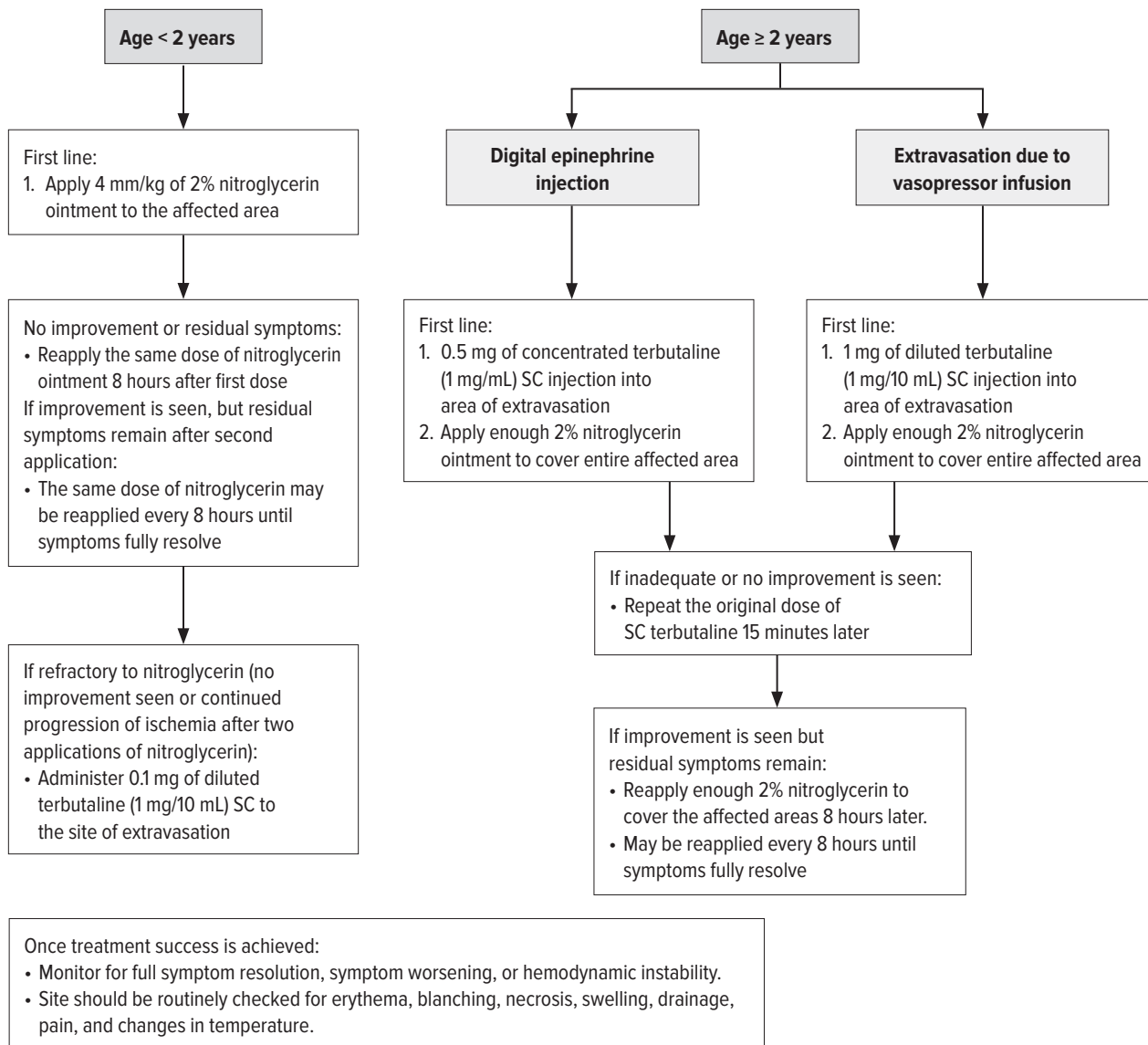
Pharmacologically, terbutaline seems to be a reasonably good option for the reversal of the intense vasoconstriction present during extravasation due to its β_2 stimulation, which leads to vasodilation. The injection formulation also seems to be ideal because it can be administered locally and directly into the site of extravasation. In the cases reviewed, terbutaline consistently worked more quickly than topical nitroglycerin, with symptoms resolving in minutes for the majority of patients. Nitroglycerin took up to one month of sustained treatment to achieve symptom resolution in one case. Terbutaline also worked in a case when topical nitroglycerin failed, further suggesting effectiveness. Nitroglycerin does not directly act on adrenergic receptors, the actual cause of the extravasation, and therefore may not be as effective as a single agent to reverse extravasation compared with terbutaline. In the reviewed cases, terbutaline had one treatment failure in a setting of delayed treatment initiation, while nitroglycerin had one failure and one incomplete recovery despite immediate treatment initiation.

Pharmacologically, the effects of topical nitroglycerin after absorption should be similar in both adults and pediatric patients; however, extent of absorption may differ because body surface area, skin integrity, and water content differ between the two age groups. Dosing, absorption, and possibly efficacy could

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Figure 1 Suggested Treatment Algorithm for the Management Of Vasopressor Extravasation in the Absence of Phentolamine

Immediately stop the infusion, aspirate back 3–5 mL of fluid if possible. Apply warm compresses and elevate the area.



be measurably different. It is also unknown if this preparation could be used on broken skin safely and effectively. This is a potential situation in which administration by injection may be ideal, therefore making terbutaline the preferred choice. On the other hand, a possible benefit of using topical nitroglycerin is that the remainder can be wiped away if signs of toxicity are noted before it is completely absorbed, which would be ideal in neonatal patients. It can also be applied to large areas of the body in the case of extravasation that affects entire limbs, which was seen in many of the neonatal cases.

It is not possible to determine the superiority of either therapy because there are no direct comparative trials. Although more

data have been published on nitroglycerin than terbutaline, it is necessary to acknowledge the possibility of publication bias in this review. It is likely that more cases exist but were never published or reported. It is also possible that more data exist for topical nitroglycerin not because it is superior, but simply because more case reports were published, causing more people to continue to use this option rather than other alternatives, such as terbutaline. In addition, the majority of cases available involved epinephrine and dopamine extravasation, while there were far less data for alternative management of norepinephrine and vasopressin extravasation. Therefore, we may not be able to confidently generalize our recommenda-

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tions to all vasopressors. Similarly, further publication bias is possible due to failure to locate all existing case reports during the literature review process.

Overall, it is clear that both terbutaline and nitroglycerin may be acceptable options for the treatment of vasopressor extravasation, and insufficient evidence is available to suggest superiority of one agent over the other. However, after thorough review of the literature, we recommend a possible treatment algorithm in Figure 1. Prompt initiation of both pharmacological and nonpharmacological treatment is essential for optimal treatment success and avoidance of permanent tissue injury.

It is essential to consider nonpharmacological options while pharmacological management is being prepared and throughout treatment. Immediate discontinuation of the infusion is vital. The catheter should remain in place so that aspiration of 3–5 mL of fluid may be attempted in order to remove the vesicant and avoid further tissue damage. Elevating the affected area and applying warm compresses can reduce symptoms and minimize further complications. Cold compresses are not recommended for extravasation with vasopressors because they can lead to further vasoconstriction.^{1–5}

For patients 2 years of age and older who experience extravasation due to infusion of vasopressors in the absence of phentolamine, the first-line alternative pharmacological treatment should be combined administration of 1 mg of diluted SC terbutaline (1 mg/10 mL), followed by topical application of a thin film of 2% nitroglycerin ointment over the entire ischemic area. This combination of two different mechanisms for vasodilation is likely to be the most effective approach for relieving extravasation quickly and preventing further tissue ischemia. Nitroglycerin was commonly used in combination with phentolamine, which has a mechanism of action that works on adrenergic receptors, so it is reasonable to use it in combination with terbutaline, a drug with a mechanism of action that is also based on adrenergic receptor activity.^{6,20,22,24,25}

For patients 2 years of age and older who experience accidental digital epinephrine injections in the absence of phentolamine, the recommended approach is to inject 0.5 mg of concentrated SC terbutaline (1 mg/1 mL), followed by applying a thin film of 2% nitroglycerin ointment over the entire ischemic area. The use of concentrated terbutaline (1 mg/1 mL) is ideal for digital extravasation because the same amount of drug can be delivered via a smaller volume, as the area of extravasation is smaller than on the extremities.

If initial treatment fails to resolve symptoms for either peripheral infusion or digital injection, a second equivalent dose of terbutaline may be repeated 15 minutes later. If improvement is seen but residual symptoms remain, nitroglycerin ointment may be reapplied every eight hours until symptoms subside and perfusion is fully restored.

For vasopressor extravasation in neonates and children younger than 2 years of age, terbutaline cannot be recommended as a first-line agent because no case reports are available to assess the safety and efficacy of its use in this age group. Therefore, the first-line alternative agent for neonates is the topical application of 4 mm/kg of 2% nitroglycerin ointment to the ischemic area. If symptoms do not resolve, an equal dose can be reapplied in eight hours and continued as needed until perfusion is fully restored. For patients who are refractory to

nitroglycerin treatment, defined as no improvement or progression of ischemia after two applications of nitroglycerin, it may be reasonable to attempt SC administration of 0.1 mg of diluted terbutaline (1 mg/10 mL) to the site of extravasation with continuous monitoring. Although evidence is lacking, this treatment option may be promising in the case of refractory extravasation.

Close monitoring is vital for the safety of the patient and effective management of extravasation. Signs of treatment success and restored perfusion, signs of treatment failure or progression of ischemia, and signs of hemodynamic instability should be monitored closely to dictate further treatment. The site should be checked routinely for erythema, blanching, necrosis, swelling, drainage, pain, and temperature.¹¹ A plastic surgeon should be consulted if pain persists, or if necrosis, ulceration, or compartment syndrome are evident after nonpharmacological and pharmacological treatment.¹¹

CONCLUSION

Although there are limited data for alternative treatment options to be used in vasopressor extravasation, there is reasonable evidence to support a treatment algorithm to be used in the absence of phentolamine. Prevention of extravasation, publishing case reports regarding the treatment used and outcome produced, and further research are the keys to finding a standard treatment option for the management of this adverse event.

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